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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/539,735	03/30/2000	James L. Brown	DHI-03864	8888

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EXAMINER
NOLAN, PATRICK J

ART UNIT	PAPER NUMBER
1644	20

DATE MAILED: 02/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/539,735	Brown et al.
Examiner	**Art Unit**
Patrick J. Nolan	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 6, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-16, and 18-21* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-16, and 18-21* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 18
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. Claims 1, 3-16, 18 and newly added claims 19-21 are pending.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-6-02 has been entered.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 19-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In claims 19-21 to be able to determine the luciferase activity of the said CHO-Rluc cells one of skill in the art would be required to perform an assay on said CHO-Rluc with bovine thyroid stimulating hormone on the same cells that were stimulated with thyroid stimulating autoantibodies as is required by claim 1. However, in Applicant's originally filed specification and claims the CHO-Rluc cells were either incubated with bovine TSH or thyroid stimulating autoantibodies, not both.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 3-16 and 18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Evans et al. (17 on the IDS), in view of Yamashiro et al. (49 on the IDS), all of record for reasons set forth in Paper Nos. 10 and 14.

The declaration under 37 CFR 1.132 filed 12-6-02 is insufficient to overcome the rejection of claims 1, 3-16 and 18 based upon 35 USC 103 as set forth in the last Office action for reasons set forth below.

Applicant's arguments filed 12-6-02 have been fully considered but are not found persuasive. Applicant arguments are directed to the declaration filed by Dr. Kohn. The Examiner's response to the declaration is set forth below.

A. Declarant argues that intracellular signal transduction is cell and stage specific. They further argue that it is a gross oversimplification and a scientific error to assume, as the Examiner does that responses(such as elevation of cAMP levels and the effect of PEG on these levels) that are mediated by intracellular signal transduction via the TSH receptor would be same in two different cell types, porcine thyroid cells vs hamster ovary cells.

However, Kimura et al., provided by Applicant specifically teaches that "In all the thyroid cells systems [primary cultures from dog, calf, sheep and human and cell lines FRTL-5, WRT and PC Cl3 derived from rats] TSH activates the Gsα/adenylyl cyclase/cAMP cascade." In addition Applicant's own specification teaches that CHO-Rluc cells, causes an increase in cAMP levels via a Gsα protein coupled to the TSH receptor which activates adenylyl cyclase which directly cause the generation of cAMP, see Applicant's specification at page 4, lines 11-15. Furthermore, the motivation behind the CHO-Rluc cell line was to generate a cell line that was more stable than primary cell cultures but maintained the generation of the same second messenger, cAMP in response to thyroid stimulating autoantibodies, see Applicant's own specification, section Background. Since activating the TSH receptor causes cAMP generation via Gsα and adenylyl cyclase in all thyroid cells derived from seven different sources the mechanism by which cAMP generation occurs in thyroid TSH receptor cells appears to be universal and CHO-Rluc cells generate cAMP by the same mechanism, the demonstration of PEG cAMP stimulation in porcine thyroid cells would be reasonably expected to succeed in CHO-Rluc cells.

B. Declarant argues that the intracellular signaling pathway(s) induced by binding of a ligand to the TSH receptor is unpredictable in the same cell type from different animals.

The reference used to support this allegation, Kimura et al., teaches that after cAMP is generated by a single mechanism, the Gsα/adenylyl cyclase/cAMP cascade, the secondary cellular effects are widely diverse, but not how cAMP was generated, which is what

is at issue.

C. The intracellular signaling pathway induced by binding of a ligand to the TSH receptor is unpredictable in the same cell type at different stages of differentiation.

In the paper Declarant cites, Bell et al., preadipocytes were tested for reactivity to TSH and were found not to produce cAMP in response to TSH binding to the receptor, however mature adipocytes as would be found in a mature human being did respond to TSH binding to the receptor with the generation of cAMP. This reference is not a close correlative to the claimed invention for two reasons, the purpose of the invention is to detect thyroid stimulating autoantibodies in mature humans to detect graves disease, a disease that is predominantly caused by autoantibodies stimulating the thyroid not fat tissue. Secondarily, it is well recognized that during development certain genes are turned on and off at different times during development, the pre-adipocytes are not representative of what one of skill in the art would recognize to be pertinent in comparing TSH activity in adult humans. Lastly, Bell states conclusively that "The well established TSH signal transduction pathway in thyrocytes is characterized by G protein activation of adenylyl cyclase, leading to elevated cAMP levels...".

D. The intracellular signaling pathway induced by binding of different ligands to the TSH receptor is unpredictable in the same cell.

This is not persuasive because both Evans et al., and Yamashiro et al., both teach that thyroid stimulating autoantibodies have the same effect in the porcine thyroid cell and CHO-Rluc cells, they both increase cAMP levels via a Gsα protein coupled to the TSH receptor which activates adenylyl cyclase which directly cause the generation of cAMP, see Kimura et al., and Applicant's specification at page 4, lines 11-15.

E. The mechanism of action of PEG on cAMP is unknown and therefore its effect on cAMP in different cells is unpredictable.

This is not persuasive for two reasons. First, how PEG works is not required to make an obvious rejection under 35 USC 103. Secondarily, all of the components in the generation of cAMP in the Yamashiro et al., assay and the Evans et al., assay appear to be functionally identical. Both assay systems use thyroid stimulating antibodies to bind to the TSH receptor, wherein said binding activates the TSH receptor to bind to G protein, wherein said Gsα protein then activates adenylyl cyclase which then generates cAMP. Since all the components are functionally identical, the effects of PEG on cAMP generation in porcine thyroid cells would be reasonably expected to also occur in CHO-Rluc cells.

F. cAMP-signaled gene expression is unpredictable in different

cells.

This argument is not persuasive because the difference between the primary reference, Evans et al., and the secondary reference Yamashiro et al., is not whether or not cAMP is going to induce gene expression. Evans et al., clearly teaches the transfection of CHO-R cells with genes that in the presence of CREB proteins which are phosphorylated due to cAMP activated PKA causes efficient gene expression and luminescence. What is at issue is whether there was a reasonable expectation of success that PEG would increase cAMP levels in CHO-Rluc as it did porcine cells.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick Nolan whose telephone number is (703) 305-1987. The examiner can normally be reached on Monday through Friday from 8:30 am to 4:30 pm.

7. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (703) 305-3973. The FAX number for our group, 1644, is (703) 305-7939. Any inquiry of a general nature relating to the status of this application or proceeding should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Patrick J. Nolan, Ph.D.
Primary Examiner, Group 1640
February 23, 2003